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| 1632 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/993,564 | NEWMAN, STUART A. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4,6,7,10,28,30,31,33,34,59,72,73,75-77 and 91-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,10,28,30,31,33,34,59,72,73,75-77 and 91-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/02, 8/26/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed February 9, 2004 have been fully considered but they are not persuasive. Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are pending.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-50 of copending Application No. 10/308,135 for reasons or record.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has stated that a terminal disclaimer will be submitted should claims 37-50 of '135 be allowed.

***Claim Rejections-35 U.S.C. 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 remains rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entries HTB 157, 158, and 160 for reasons of record. It is noted that ATCC entries HTB 157, 158 and 160 are isolated human embryonic and fetal cell lines.

Claim 10 stands rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378, designated MA-104 cells for reasons of record. It is noted that ATCC entry CRL-2378 is a Rhesus monkey embryonic kidney cell line.

It is noted that applicant did not respond to the rejection of claim 10 under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378. However, the examiner will assume that applicant intended the same argument for this rejection as for the argument presented for rejection of claim 10 under 35 U.S.C. 102(b) as anticipated by ATCC entries HTB 157, 158 and 160.

Applicant argues that the ATCC cell lines do not anticipate claim 10 because the cell lines would not be immunologically tolerated by both human and nonhuman primate species. Applicant argues that the specification provides a definition of the phrase "immunologically tolerated" by using the phrase as it was known in the art at the time of filing. Applicant argues that Gustafson provides evidence of sheep-goat chimeras being "immunologically tolerant" in that the chimeras tolerate the cells of both species without immunosuppressive drugs. Applicant argues that it was known in the art at the time of filing that a mixed lymphocyte response was not performed under the influences of immunosuppressive drugs. Applicant argues that the ability of tissues of the chimeras to be tolerated by either parental species is due to the immune system of the chimera becoming

chimeric during development. Applicant argues Fehilly et al and Meinecke-Tillman demonstrate tolerance where the single species mother tolerates the chimeric sheep-goat embryo in the absence of immunosuppressive drugs. Applicant argues that human and nonhuman primate species would not both immunologically tolerate the human or nonhuman primate cell line of the prior art presently claimed unless immunosuppressive drugs were used. These arguments are not persuasive.

The specification does not provide a definition of "immunologically tolerated" or "immunologically tolerant." Given this lack of definition, the broadest reasonable meaning of the terms is being used in the present examination. Thus, "immunologically tolerated" or "immunologically tolerant" is defined as the acceptance of a cell, tissue or organ for some period of time prior to rejection, and the cell not undergoing hyperacute rejection as is observed with xenografts. The specification mentions immune tolerance, which is known in the art of immunology to be the situation where an individual's immune system does not recognize the individual's own cells, tissues and organs as foreign (specification, page 11). This concept is sometime referred as "self recognition." It is the mechanism of "self" that permits success in autologous, within the same person, transplantation. However, there is no evidence in the specification or in the art at the time of filing that this process of self-recognition would have taken place during the development of the claimed human/nonhuman primate embryos. Gustafson, cited by applicant in their arguments, clearly discloses that skin grafts between chimeric and nonchimeric siblings of the chimeric animals were accepted for a period of time and subsequently underwent rejection (Gustafson, page 162, Table 4). Disclosed in Gustafson is the initial acceptance, followed by rejection, of grafts from 87-C to 88-G (chimera no. 87 to goat no. 88), 79-C to 80-G and d 82-C to 83-G (page 163, parag. 4, lines 1-2, parag. 6, lines 4-6; and page 164, parag. 1, lines 4-6). Thus, the chimeras disclosed in Gustafson, regardless of mixed lymphocyte

response, provide cells that are "immunologically tolerated" by the first and second species of the chimera for a period of time, followed by rejection. That is the grafts were initially "immunologically tolerated" or the animals initially "immunologically tolerated" the grafts. This teaching supports the examiner's definition, above, of "immunologically tolerated" or "immunologically tolerant." Gustafson's results, also, demonstrate that "self recognition" does not occur in the chimeric goat x sheep animals. If "self" had been recognized, there would not have been any rejection of grafted tissues. Furthermore, the specification at page 11, states that Gustafson "found that *some* normal sheep and goat siblings of sheep-goat chimeras were able to tolerate skin grafts from their chimeric siblings and exhibited immune tolerance to their chimeric siblings as measured by the mixed lymphocyte response (MLR)" (specification, page 11, lines 15-18). The graft results presented in Gustafson were, as applicant stated, without immunosuppression. However, the grafts were ultimately rejected. Gustafson thus does not provide any evidence that the cells of the cited ATCC entries would have not had the same degree of "immunological tolerance" when grafted to both a human and nonhuman animal species. Therefore, it is maintained that the cell line of the cited prior art would have been "immunologically tolerated" given the graft data of Gustafson and the meaning of the term given by the examiner.

Fehilly et al provides evidence that successful sheep x goat chimera development was associated with the placenta being composed primarily of cells that were of the same species as the foster mother (Fehilly, page 636, col. 2, parag. 1). In other words the foster mothers "permitted" chimera development only when the placenta was composed of cells that were of the same species as the mother or were mostly composed of cells of the same species as the mother. Immunosuppressive drugs were not needed and fetal loss did not occur because the mother recognized the placenta as "self." When the placenta was composed of cells that matched the mother's species, the immune system of the foster

mother did not mount a response to the chimeric embryo/fetus' placenta because the cells of the placenta were not recognized as foreign. There was no need for the placenta to be immunologically tolerated; it was seen as immunologically the same, or sufficiently the same to be tolerated. However, it should be noted that Fehilly also teaches that when the placenta was composed mostly of cells of the other parental species, fetal loss was high. Meinecke-Tillman states that development of a chimeric embryo only occurs when there is a protective barrier to overcome recognition of the foreign fetus by the mother of the other species (Meinecke-Tillman, page 638, col. 1, parag. 1, lines 1-4). Thus, neither Fehilly nor Meinecke-Tillman support the concept a foster mother exhibits immunological tolerance toward implanted chimeric embryos. To the contrary, Fehilly and Meinecke-Tillman teach that there is no tolerance if the placental cells are not of the same species as the foster mother, and the foster mother will lose the chimeric fetus if the placenta contains too many cells of the other parental species.

Applicant states that it is "well-known in the art that tolerance of foreign cells without the need of immunosuppressants is the commonly accepted criterion." Applicant argues that references by the examiner to Starzl et al and Lambrigts et al as evidence of cell lines from different species that are immunologically tolerant of each other is misplaced. Applicant states that in Starzl, humans were only tolerant of baboon cells when immunosuppressive drugs were administered. Applicant cites Bartholomew et al as evidence that different primates usually do not tolerate on another's cells and tissue without immunosuppression. Applicant argues that the ATCC cell lines, therefore, would not be expected to be tolerated by both human and nonhuman primates species in the absence of immunosuppressive drugs. These arguments are not persuasive.

Applicant does not provide any evidence in support of the assertion that "immunological tolerance" or "immunologically tolerated" are only measured in the absence

of immunosuppressive drugs. Starzl and Lambrigts do not provide any information on the length of graft acceptance in the absence of immunosuppression. Gustafson, as discussed above, performed analysis of grafted tissues between sheep x goat chimeras in the absence of immunosuppressive drugs, but Gustafson does not say that tolerance is only determined in the absence of immunosuppressive drugs. Bartholomew discusses induced tolerance using the mixed chimerism approach (Bartholomew, page 1708, col. 2, parag. 2, lines 1-4), which would indicate that tolerance induced by outside factors is still regarded as making the tissues transplanted immunologically tolerated.

Further, Bartholomew teaches methods to overcome host versus graft disease for replacement transplantation of organs between primates. This does not teach that left untreated, the transplanted organs would not be tolerated for some length of time in a non-immunosuppressed individual. Given Gustafson, and applicant's reliance on the reference, demonstrating that skin grafts from chimeric animals to its single species siblings are rejected, immunologically tolerated would mean tolerated for some period of time before rejection. Applicant's arguments hinge on a term, immunologically tolerated, that is not defined in the specification and is not defined in the art. There is no evidence of record that refutes the examiner's interpretation of "immunologically tolerated" as stated above and used in the examination of the present claims claim 10 to include tolerance for any period of time with or without immunosuppressive drug use. Based upon the art and evidence of record, the cells of the prior art could have reasonable been expected to survive for some period of time prior to rejection. Thus the broadest reasonable definition, discussed above, has been applied to claim 10.

***Claim Rejections - 35 U.S.C. 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The enablement rejection, in summary, is that the specification fails to provide sufficient guidance to make and use human/nonhuman primate chimeric embryos. Neither the art at the time of filing nor the present specification provide the requisite guidance as to the methodology that would lead to the production of these chimeric embryos or their use in the disclosed production of chimeric human/nonhuman primate animals or the cell line of claim 10 without an undue amount of experimentation or with a predictable degree of success.

Applicant argues that techniques were known in the art at the time of filing for the production of interspecific chimeric embryos, and for the culturing of these chimeric embryos. Applicant argues that these techniques could be applied to the production of human/nonhuman primate chimeric embryos without undue experimentation. Further, applicant argues methodology of the culture of nonhuman primate and human embryos was also known at the time of filing. As evidence, applicant cites several research articles available to the skilled artisan at the time of filing. Fehilly (1984) and Meinecke-Tillman (1984), applicant argues, teaches the production of interspecific chimeric sheep x goat embryos. Applicant argues that Fehilly teaches three techniques to produce sheep x goat chimeras: combining single 4-cell goat embryo blastomeres with single 4-cell sheep embryo blastomeres or with single 8-cell sheep embryo blastomeres; surrounding an 8-cell goat embryo absent a zona pellucida with blastomeres of three 8-cell sheep embryos or

surrounding a 8-cell sheep embryo with blastomeres of three 8-cell goat embryos, and inserting inner cell mass cells and polar trophoectoderm cells from an 8-day goat embryo or 8-day sheep embryo into 8-day sheep blastocyst or goat blastocyst, respectively. Applicant argues that Meinecke-Tillman transferred the chimeric embryos and brought to term sheep-lamb and goat-lamb interspecific chimeras. Applicant argues that Meinecke-Tillman produced interspecific sheep x goat embryos by combining one sheep blastomere from a 4-cell stage embryo with two goat blastomeres or two sheep blastomeres from the "early" 8-cell stage with two goat blastomeres of the "late" 8-cell stage. Applicant argues that several references were known in the art at the time of filing that taught generic methods of mammalian embryo culture and producing mammalian embryos. Applicant cites Pope et al (1982), Gould (1983), Pope (1984), Fourie (1987), Pope (1997), US Patent 6,211,429 (Machaty), US Patent 6,376,743 (Yanagimachi), Homa (1994) and Herbert (1995). Applicant argues that the methods disclosed in these references could be applied to the production of human/nonhuman primate chimeric embryos without undue experimentation. These arguments are not persuasive.

It should be noted that the specification does not provide a definition of applicant's meaning of the term "chimeric animal" or "chimeric animal embryo." However, Applicant states in the response of February 9, 2004 the chimeric animal embryo claimed would "develop while incorporating both human and nonhuman primate cells into all of the organs of the resulting chimeric animal" (response, page 12, parag. 1, lines 7-9). This definition is not supported by the teachings of the art at the time of filing which defined chimeric animal without specifying parental cell contribution to organs or tissues of the chimera. The art defined a chimeric animal as "consisting of a mixture of cells derived from more than one animal; and "produced by a mixing of cells from the early stages of development of two different embryos" (Rossant (1982), page 1241, col. 2, parag. 1, lines 5-12). Thus, the art's

definition encompasses applicant's definition but includes chimerism found in some tissues but not others, or where a tissue is composed of one parental cell type while other tissues are composed of the other parental cell type or mixtures of parental cell types. Further, as discussed in detail below, the sheep – goat chimera art does not support a chimeric embryo developing to provide cell contributions from both species through out all of the resulting chimeric animal's organs and tissues.

Using either applicant's definition of chimeric embryo/animal or the broader definition provided by the art at the time of filing, the art cited by applicant in the response does not enable the claimed chimeric embryos (which, as argued by applicant, encompass chimeric embryos from the earliest 2-, 4-, or 8-cell stage through the development of the chimeric embryo until it becomes a chimeric animal). The results reported in Fehilly clearly support a lack of enablement of the claimed chimeric embryos. There is no predictability that parental cells in a chimeric embryo will contribute to all the organs and tissues in a resulting chimera or that the parental cell will contribute to any particular organs or tissues in a resulting chimera. Fehilly produced sheep x goat chimeric embryos, using the method as stated by applicant, which when implanted into surrogate mothers resulted in 8 interspecies chimeras (page 635, Table 1). Only one animal was described as having two chimeric tissues, and that one was a coat and blood protein chimera (See Fehilly, page 636, col. 20.). The other chimeras are each described as being a coat chimera, that is, these sheep-goats had coat/skin contributions from each parent. Meinecke-Tillman teaches as applicant has described, but the animals born are not tissue chimeras. The author states "cytogenetic analysis, hemoglobin and transferring typing, blood group serology, polyacrylamide gel electrophoretic analysis of blood and muscle proteins and breeding experiments gave no indications of chimerism" (Meinecke-Tillman, page 638, col. 1, parag. 1). Thus, there is no guidance in Fehilly or Meinecke-Tillman for producing a chimeric

embryo that predictably produces a chimeric animal regardless of parental cell contributions to the animal's tissues and organs. Both references actually support the unpredictability of producing chimeric animals of any definition in that neither reference provided direction for obtaining reproducibly a chimeric human/nonhuman primate animal whose organs and tissues were of any particular parental cell composition from a chimeric human/nonhuman primate embryo. Rossant teaches the production of chimeras of separate mouse species from chimeric mouse embryos; obviously the mice are of the same genus. The present animals would not be of the same genus or species. Further, Rossant (1983) taught the degree of chimerism or mosiacism in adult chimeric mice varied (Rossant, page 196, Table 2). Chimera 2 has only mosiacism in leg muscle, chimera 3 demonstrated blood, brain and leg muscle mosiacism, and other chimera demonstrated mosiacism in all tissues analyzed but the degree of mosiacism varied. Thus, Rossant does not support the enablement of the claimed chimeric human/nonhuman primate embryos as the degree of chimerism between individual mice was unpredictable, and without any apparent means of chimerism control by the artisan. Especially Rossant supports the unpredictability of obtaining chimerism in all the organs/tissues of the chimera. Thus, the production of chimeric human/nonhuman primate embryos that develop into chimeric animals having both human and nonhuman primate cells in all or some of their tissues/organs is not predictable without undue experimentation given the teachings in the art at the time of filing and the lack of guidance in the specification.

The additional references, Pope (1982), Gould, Pope (1984), Fourie, Pope (1997), US Patent 6,211,429 (Machaty), US Patent 6,376,743 (Yanagimachi), Homa (1994) and Herbert (1995), each teach various methods of culturing or producing by IVF primate embryos or human embryos. While these references may teach such methods, none of the

methods address the unpredictability in using the chimeric embryos of the claims to produce a chimeric human/nonhuman primate animal of either applicant's or the art's definition.

Applicant argues that the specification was also enabled for the production of chimeric human/nonhuman primate embryos using human and nonhuman primate embryonic stem cells as the methods of isolating and culturing these stem cells were known at the time of filing. Applicant argues that Thomson (1995) teaches the isolation of an ES cell line from the embryo of a rhesus monkey and the isolation of human ES cells (1998). Applicant argues the ES cell lines were isolated using existing techniques without undue experimentation. Applicant argues that prior to the present filing date, the isolation of ES-like cells from human embryos was known (Bongso et al (1994)). Applicant argues that Bradley (1984) discloses techniques that can be used to produce interspecific chimeric embryos, and that Bradley also teaches that the combination of ES cells from the same or different species will result in normal development of the embryo. Applicant argues that Nagy et al (1993) teaches the use of early passage ES cells to produce mice that are completely ES cell derived by combining mouse ES cells with defective mouse embryos. Applicant argues that Goldstein (2002) discloses human embryo ES cells implanted into chick embryos to make human/chicken chimeric embryos. These arguments are not persuasive.

Neither Applicant's assertion that the chimeric embryo claimed would "develop while incorporating both human and nonhuman primate cells into all of the organs of the resulting chimeric animal" (response, page 12, parag. 1, lines 7-9) nor the art's broader definition is enabled by the specification nor applicant's cited art. As taught by Fehilly et al and Meinecke-Tillman et al, as discussed above, the parental contribution to organs and tissues of sheep x goat chimeras is unpredictable when chimeric embryos are implanted in a surrogate mother. Whereas Thomson (1995 and 1998) and Bongos (1994) each teach

nonhuman primate or human ES cell or ES-like cell isolation and culture, none of these references provide methodology for the production of human/nonhuman primate chimeric embryos that can produce a chimeric animal having all of its tissues/organs comprised of cells from both parents. Additionally, Nagy discloses the cloning of mice from mouse ES cells using mouse tetraploid embryos. These teachings are not comparable to the present claims as the embryos are same species, mouse, and not separate genus species as presently claimed. Nagy, therefore, does not provide any guidance to the production of chimeric embryos that are capable of producing chimeric human/nonhuman primate animals with tissue contributions from two separate species. There is no evidence on this record that to make a human/nonhuman primate chimeric embryo all one would need is access to ES cells. Goldstein produced chimeric human/chick embryos by a method not contemplated by the specification. At no place does the specification discuss injecting human or primate embryonic cells into an embryo that already had distinct organ system formation (specification, pages 1-5). Goldstein states that human ES cells were injected into the trunk region of 1.5 to 2 day chick embryos (Goldstein, page 81, col. 1, parag. 1, lines 1-3). Goldstein distinguishes the work therein from applicant's methodology in stating "these experiments are also different from those attempting to produce true chimeric embryos where stems cells are mixed or injected into intact embryos at the blastula/gastrula stage and could potentially make a major contribution to many of the host tissues" (Goldstein, page 83, col. 2, lines 8-13). Finally, the chimeric mice produced by Bradley are chimeric for other mouse strains. Thus, these animals are not relevant to presently claimed chimeric human/nonhuman primate animals as Bradley's mice are produced by inserting a blastomere from an embryo of one mouse strain into a blastocyst of a second mouse strain. Bradley's experiments were to animals of the same genus-species; the only differences

were strain differences. Nothing in Bradley offers guidance on producing chimeric embryos of separate genus, which lead to the production of chimeric animals.

Applicant asserts that at least one credible utility has been identified in the specification by describing how the present chimeric embryos and animals can be used in toxicology assays. Applicant argues that the specification states that the invention would be useful to determine the teratogenic and developmental toxicity of various chemicals. Applicant argues that Naruse et al and Prati et al describe methodology for using chimeric embryos for teratologic screening. These arguments are not persuasive.

Naruse is directed to toxicology assays using mammalian embryos, such as the exemplified mice, of a single species and not chimeric embryos (Naruse, page 196). Prati is not of record and cannot, therefore, be considered. With regard to applicant's statement that the claimed chimeric embryos can be used in toxicology assays, applicant has not provided any evidence or reasoning as how results obtained from such studies would be useful. It is not seen, and the specification does not teach, when, under what conditions or if ever any data obtained from the embryo-based assay would be useful to the skilled artisan. The results would be pertinent to chimeric embryos and not embryos of only one of the species comprising the embryos. Without guidance as to the use of the human/nonhuman primate embryo as toxicology assay, the embryo has no enabled use in this capacity.

Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The claims lack written description because the specification fails to describe the claimed embryos or the embryo required to produce the embryonic cell line of claim 10 sufficient to reasonable convey that they had possession of the invention at the time of filing.

Applicant argues that the specification describes the claimed chimeric human/nonhuman primate chimeric embryo using terms in the same manner as they are well known and regularly used in the art. Applicant argues that describing and referring to the present invention as a chimeric embryo is sufficient to demonstrate possession of the invention at the time of filing. Applicant argues that at the time of filing, chimeric embryo was known in the art to mean an embryo, at all stages of development, comprised of two genetically distinct types of cells. Applicant argues that several scientific articles describe chimeric embryos and conveys the art accepted meaning. Applicant argues that Fehilly demonstrates sheep x goat chimeras produced by combining sheep and goat embryonic cells, and that these sheep x goat chimeric embryos develop into chimeric animals. Applicant argues that the term "chimera" as used in the art and present specification refers to an animal, which develops from an embryo made from two genetically distinct species or two different species. Applicant argues that Meinecke-Tillman describes the production of interspecific chimeric embryos by combining blastomeres from a 4 or 8-cell sheep embryo with an 8-cell goat embryo. (A blastomere is one of the cells that make up a pre-implantation embryo.) Meinecke-Tillman, applicant argues, then produced sheep-goat and goat-sheep chimeras from these embryos comprising cells of both sheep and goats. Applicant argues that chimeric embryo refers to an embryo, at all stages of development, made from cells of two distinct species and chimera refers to the animal, which develops from that embryo. Applicant argues that Rossant demonstrates somatic and germ line mosiacism in interspecific chimeras between *Mus musculus* and *Mus caroli*, and that cells

from the two species coexist and interact normally in all tissues studied. These arguments are not persuasive.

Applicant states the chimeric animal embryo claimed would "develop while incorporating both human and nonhuman primate cells into all of the organs of the resulting chimeric animal" (response, page 12, parag. 1, lines 7-9). However, the specification does not provide this or any other definition of "chimeric". Additionally, this definition, as provided in the response, does not appear to be consistent with the definition used in the art. The art at the time of filing defined chimeric animal, and by extension, chimeric embryo as "consisting of a mixture of cells derived from more than one animal; and "produced by a mixing of cells from the early stages of development of two different embryos (Rossant (1982), page 1241, col. 2, parag. 1, lines 5-12). Given either Rossant's definition or applicant's definition in the response, the specification does not show possession by applicant at the time of filing for chimeric human/nonhuman primate embryos at all stages of development. In late stage embryos, where organogenesis has begun, there is no description of these embryos so that the skilled artisan could envision the contribution of each parent cell-type to the various pre-organ systems of the embryos. If one reviews the art of chimeric animal production, which is more reflective of the late-stage embryo, the lack of written description becomes apparent.

Fehilly teaches that 3 out of 7 (experiment 1a) animals were overt sheep x goat chimeras based upon coat characteristics. These animals had the general appearance of lambs but the fleece had transverse bands and patching of hair contrasting sharply with the surrounding densely cultured wool. The hairy bands were thought to represent goat tissue. In another experiment (2b), the animals had the same general appearance as kids, but along the neck, shoulders and backs of the animals, curly sheep's wool was seen instead of normal straight goat hair. Fehilly teaches that of all the live born sheep x goat chimera,

each identified by coat composition, only one of the chimeric animals demonstrated any degree of chimerism in blood proteins (Fehilly, page 636, col. 2, parag. 1). The goat-lamb, that is a goat kid produced by a sheep mother implanted with a sheep–goat chimeric embryo, described in Meinecke-Tillman exhibited no chimerism by cytogenetic analysis, hemoglobin and transferring typing, blood group serology, polyacrylamide gel electrophoretic analysis of blood and muscle proteins and breeding experiments (Meinecke-Tillman, page 638, col. 1, parag. 1.) Thus, Fehilly and Meinecke-Tillman fail to support applicant's arguments. The chimeric embryos of Fehilly and Meinecke-Tillman were not composed of tissues that contained cells from both parental complements, as the chimeric embryos did not give rise to a totally chimeric animal in Fehilly or a chimeric animal at all in Meinecke-Tillman. The Meinecke-Tillman abstract, last line, clearly states that the goat – lamb is actually a kid born to an ewe.

The degree of chimerism or mosiacism in adult chimera, as demonstrated by Rossant (1983), varies widely among the animals analyzed (Rossant, page 196, Table 2). Chimera 2 has only mosiacism in leg muscle, chimera 3 demonstrated blood, brain and leg muscle mosiacism, and other chimera demonstrated mosiacism in all tissues analyzed but the degree of mosiacism varied. Also, the chimeras produced by Rossant are materially different from those claimed; the chimera Rossant are of the same genus but of different species. One would expect, perhaps, a better rate of chimera formation when the parental cells are different species of the same genus, rather than as presently claimed where the parents are of different genus and species.

The composition of the late-stage embryo would thus be reflected in the resulting animal, and as a description of the animal could not be envisioned, a description of the chimeric embryo could also not be envisioned. None of Fehilly et al, Meinecke-Tillman et al or Rossant et al convey that the art, at the time of filing, described chimeric embryos

sufficiently that the skilled artisan could have envisioned applicant's claimed chimeric embryos sufficiently to deem that applicant had possession of the embryos at the time of filing. Thus, the particular make up of the claimed chimeric human/nonhuman primate embryos could not be visualized until a reduction to practice had occurred. The specification does not describe the degree of mosiacism in the various embryonic tissues and/or organs by words or example; as exemplified in Fehilly et al., Meinecke-Tillman et al. and Rossant et al., mosiacism is taught by the art to variable. Thus, the skilled artisan, reading the specification and with the knowledge of Fehilly et al, Meinecke-Tillman et al or Rossant et al, could not envision the claimed chimeric human/nonhuman primate embryos. Further, none of the descriptions of the prior art experiments are reported to suggest the composition of a human/nonhuman primate chimera embryo. The specification does not provide evidence that those of skill in the art would have interpreted these prior art experiments as representative of a human/nonhuman primate chimeric embryo. Thus the specification would not have conveyed possession by applicant of the claimed chimeric embryos at the time of filing. The claims still fail to meet the criteria for written description at the time of filing.

Applicant argues that the term "chimeric embryo" is used to describe a very broad range of embryonic development starting with the earliest 2, 4, or 8-cell stage through the development of the chimeric embryo until it becomes a chimeric animal. Applicant argues that in a similar fashion they have described their invention of a chimeric embryo as one that has developed from a human/nonhuman primate chimeric embryo, and in describing, they have used terms in a manner as used in the art. Applicant argues that they have set forth the detailed structure of the claimed invention and has demonstrated possession of a chimeric animal developed from a chimeric embryo through the use of words, which were known to a skilled artisan to refer to animals that originate from an embryo made of cells

from two distinct species. Thus, applicant states that conception and reduction to practice has occurred by the use of art terms and filing of the present application. These arguments are not persuasive.

Issue is taken with the idea that applicant has described the claimed embryo through all its stages. While the specification sets forth the means to make a chimeric human/nonhuman primate embryos, the specification does not set forth in words or example a description of the resulting embryo that demonstrates possession at the time of filing. Embryos develop extensively and range from a one-cell entity to a multicellular entity with early organ development. Extrapolating from the arguments presented above to applicant's response, there are no words that state anything as to the degree of mosiacism possessed by the chimeric embryo in any of its tissues or even in its body as a whole. Since the degree of mosiacism, as stated above, is variable among individual chimera, a reasonable expectation would have been to find equal variability in the embryo that lead to the chimera. Thus, the specification fails to convey that applicant possessed the claimed invention through words. As there are no examples of producing a chimeric embryo, there likewise is no conveyance via example. Thus, the specification fails to describe or convey that applicant possessed the claimed chimeric embryos at the time of filing.

***Claims Rejections - 35 U.S.C. 101***

35 U.S.C. 101 reads as follows: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, and 91-106 stand rejected under 35 USC 101 as being directed to non-statutory subject matter for reasons of record.

Applicant argues that the rejection is improper for two reasons: (1) the claims are not directed to a human being or a human embryo but rather a man-made chimeric embryo, and (2) even if the claims cover human beings, the statute does not restrict patentability based on whether claims embrace a human being. The arguments have been considered but are not persuasive.

Applicant argues that the claimed embryo comprises human and non-human primate cells and is therefor interspecific, neither human nor non-human. Applicant draws an analogy to the previously known sheep-goat chimera, which Applicant says was neither sheep nor goat.

The last Office action cited Starzl et al.'s report of a human patient treated with cells transplanted from a non-human primate, a baboon. The chimeric human patient did not become non-human merely by possessing some proportion of non-human primate cells. Applicant argues that Starzl's chimeric patient and the chimeric embryo of the claims can be distinguished. Applicant concedes that "the transplanting of cells to a human being would not convert the human into a non-human and change its origin," but Applicant focuses on "origin." According to Applicant, the human/non-human primate chimeric embryo of the present invention was never exclusively human in origin since it originated as a combination of cells from two different species. That is, the claimed chimeric embryo was never solely a human embryo or a non-human primate embryo, but instead was a combination of two distinct species from the beginning of its existence.

The argument based on origin is not persuasive for two reasons. First, the focus is on what is claimed, not its origin. Starzl's treated patient is chimeric because the patient comprises cells of two different species, just as the claimed embryo is chimeric because it comprises cells of two different species. The presence of some non-human cells does not make Starzl's patient non-human, and the presence of some non-human primate cells does

not make a human embryo non-human. Second, even if origin were relevant, Applicant's new explanation is inconsistent with the specification. Contrary to the argument that the claimed chimeric embryo was never exclusively human in origin, *i.e.*, that the chimeric embryo never existed as a human embryo, the specification states: "the invention relates to chimeric embryos and chimeric animals created from human embryos . . . ." See specification at page 1, lines 2-5.

Applicant argues that an interspecific animal maturing from the chimeric embryo contains cell contributions from both species throughout all its organs, regardless of whether the chimeric embryo consisted of 100 human cells and one non-human cell or vice versa. There does not appear to be a factual basis in the specification for this argument. Instead, the specification discloses that an animal developing from the chimeric embryo would be a source of human organs. See specification, sentence bridging pages 13-14. Further, as presented previously in this office action, both Fehilly et al and Meinecke-Tillman et al teach that chimeric embryos can develop into animals of chimerism limited to one organ or no chimerism (Fehilly, page 636, col. 2, parag. 1 and Meinecke-Tillman, page 638, col. 1, parag. 1). Thus based on these results, an embryo of the present claims could certainly produce an animal of only one cell type or animal predominantly of one cell type.

Applicant argues that the statute does not restrict patentability based on whether the claims cover a human being, and that the Director lacks authority to impose a limitation on patenting a human. For reasons already stated on the record, the Office does not agree that humans are patentable subject matter.

Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, and 91-106 stand rejected under 35 USC 101 as lacking patentable utility for reasons of record.

Applicant argues that the utilities proposed in the specification are specific and substantial. Rather than discuss all the proposals in the specification, Applicant limits the

response to a discussion of two utilities: toxicology assays and development studies. According to Applicant, the proposed toxicology assays and studies of embryonic development disorders are real world uses that meet the requirement for a specific and substantial utility.

The arguments are not persuasive. Even assuming toxicology studies are a critical step in the development of new drugs, the specification's proposal for toxicology studies is so general as to be meaningless. Similarly, there is no specific explanation showing that observing the development of the claimed chimeras would have any practical utility. The proposed utilities appear to be the kind of "use testing" that does not meet the statutory requirement. That is, the claimed invention has not been brought to the point where specific benefit exists in a currently available form.

***Conclusion***

Further, with regards to the allowance of claims encompassing humans, Applicant is advised that the "Consolidated Appropriations Act, 2004," contains the following provision: "Sec. 634. None of the funds appropriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism." Pub.L. 108-199, 118 Stat. 3, 101 (January 23, 2004).

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are free of the prior art. At the time of filing the prior art did not teach or suggest a human/nonhuman primate chimeric embryo as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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